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EDITORIAL COMMENT

Primary Angioplasty for Elderly Patients With Myocardial Infarction

Theory, Practice and Possibilities*

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The appropriate method of reperfusion for patients >75 years with ST-elevation acute myocardial infarction (AMI) is one of the great enigmas of acute care cardiology. The population at risk is large, comprising roughly one-third of AMI patients and more than one half of AMI mortality (1). Yet there have been no randomized trials focusing specifically on these high-risk patients who have been notably underrepresented in randomized trials. Meta-analyses of large randomized trials of thrombolytic therapy (2,3) have found diminished relative benefit from thrombolytic therapy but persistent absolute benefit, with 1.0 to 3.4 lives saved per 100 patients treated. Two large observational studies (4,5) suggest that for patients >75 years, thrombolytic therapy involves no benefit and possible harm, despite the fact that elderly thrombolytic patients actually are healthier than those managed without reperfusion therapy. Given the limitations of both randomized trials, whose protocol-controlled therapy and ideal patients are sometimes quite different from community practice, where patients tend to be older, with a longer symptom-to-presentation interval, greater comorbidity and more relative contraindications; and of observational studies, which are inherently liable to unmeasured selection bias, expert opinion has remained conflicted.

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The study by de Boer et al. (6) in this issue of the *Journal* begins to shed some light on this subject. Beginning in March 1996, for three years their Dutch hospital enrolled 87 patients >75 years who met standard criteria for thrombolytic therapy in a prospective, randomized trial comparing direct angioplasty with intravenous streptokinase. As always, the success rate of primary angioplasty depends on the reckoning method. The authors describe a success rate of 90% (37 patients, 41 attempted angioplasties); a less optimistic intention-to-treat reckoning might also include some or all of the following: one patient who died prior to angiography; two patients referred for bypass surgery after angiography; and two patients managed conservatively after angiography. Thus, the actual angioplasty success rate was between 80% (37 successful angioplasties among 46 patients randomized) and 90%. Of angioplasty patients, 51% received stents; glycoprotein IIb/IIIa inhibitors were not used.

The results are startling. The 30-day mortality was 7% in the angioplasty arm compared to 20% in the thrombolytic arm ($p = 0.04$); one-year mortality was 11% versus 29% ($p = 0.03$); and a composite end point of death, recurrent MI or stroke during 20 months of follow-up was 8% versus 17% ($p = 0.004$). The cardiology literature is replete with trials enrolling tens of thousands of patients to demonstrate an absolute 30-day mortality benefit of barely 1% and a relative benefit of 10% to 20%; this small trial showed an absolute 30-day mortality benefit of 13% and a relative benefit of 35%, which persisted unchanged for the 20-month term of the study.

The robustness of any study's findings depend on methodologic nuances. The study by de Boer et al. (6) is fairly rigorous; it enrolled nearly all eligible patients (albeit using a verbal consent that might dismay an American institutional review board), used telephone randomization and had complete follow-up for survivors. Although novel to some Americans, the choice of streptokinase as a thrombolytic agent needs no apology; this agent, if anything, is preferable to tissue plasminogen activator in the elderly, with a lower risk of catastrophic intracerebral hemorrhage and death (7). Allowing for unstable point estimates in this small study, thrombolytic 30-day mortality is comparable to most other reports, such as the 18% 30-day mortality for patients age 76 to 86 years in a large 1994 to 1995 observational study (4) and 19% in a similar subgroup of the Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO I) study (7), although considerably higher than the 11% rate for patients >80 years in GUSTO IIB (8). Angioplasty mortality also is roughly consistent with reports from other randomized trials (9,10).

The present study also has significant weaknesses. With a planned sample of 266 patients, the study was stopped early in April 1999, after enrollment of 87 patients, with a p value of 0.01 for the primary end point, a 30-day composite outcome of death, recurrent MI and stroke. The report does not describe predefined stopping criteria, scheduled interim analyses by an independent data safety and monitoring panel or statistical adjustment of the alpha threshold for multiple looks, all of which typically require a lower p value for early stopping than for tests of significance after complete enrollment. While the p value for the composite end point during 20 months of follow-up was 0.004, the p value for 30-day mortality (a less ambiguous end point) was 0.04 and some may find that the study was stopped too soon.

Like many studies of primary angioplasty, the present study also inherently involves an uncontrolled co-intervention in the percutaneous intervention arm, in that

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nearly all patients underwent angiography and 85% underwent percutaneous or surgical revascularization, compared to only 10% of patients treated with streptokinase. By comparison, in observational U.S. data, 32.5% of patients >75 years underwent revascularization within 30 days (4). The possibility that more aggressive use of predischarge noninvasive testing, angiography and revascularization would materially alter mortality among thrombolytic patients cannot be excluded.

Both of these concerns, together with the inherent limitations and potential publication bias of single-center studies, render the report by de Boer et al. (6) exploratory rather than definitive, as the authors acknowledge. However, the study is consistent with subgroup analysis of three small randomized trials of angioplasty versus thrombolytic therapy (10), which suggested special benefit for angioplasty in elderly patients with ST-elevation MI. This inference was not supported by the rigorous analysis of Holmes et al. (9), which found no evidence of age interaction in the 1,138-patient GUSTO IIb study, but this study's methods necessarily had limited power to detect nonlinear interactions such as those potentially present among elderly patients.

Although nonrandomized, retrospective studies reporting marked benefit for primary angioplasty in elderly patients have been widely published, the grave limitations of such observational comparisons are seldom acknowledged. Retrospective databases cannot identify patients who died while awaiting primary angioplasty or those in whom angioplasty was not attempted after coronary angiography, a group that comprises 10% to 19% of the primary angioplasty groups in randomized trials (11% in the study by de Boer et al. [6]) and has a mortality as high as 14.1% (11), several times the mortality of patients who actually undergo primary angioplasty. These limitations render observational studies essentially useless for fair comparison of angioplasty and thrombolytic therapy.

Even disregarding observational reports, in light of the study of de Boer et al. (6), the preponderance of the randomized trial evidence suggests a special benefit to primary angioplasty in patients >75 years—provided that patients are treated at a center whose experience, volume and door-to-balloon time approach those in the trial of de Boer et al. (6). These are large caveats. While small randomized trials have achieved median door-to-balloon intervals of about 60 min, a large community-based trial (8) had an interval of 1.9 h and observational studies have consistently found even longer times in community practice. Berger et al. (12) reported a mean door-to-treatment interval of 143 min in Medicare patients treated with direct angioplasty and Canto et al. (13) reported median door-to-balloon intervals ranging from 119 to 135 min. There is persuasive experimental and observational evidence that such delays are associated with worse survival. Berger et al. (11) reported 30-day mortality of 1.0% for GUSTO IIb patients with a randomization-to-balloon interval <60 min, 3.7% for intervals of 61 to 75 min, 4.0% for intervals of 76 to 90 min and 6.4% for intervals >90 min. Using a door-to-balloon interval of <60 min as a reference in an analysis of data from the National Registry of Myocardial Infarction (NRMI), Cannon et al. (14) found a multivariate odds ratio for in-hospital mortality of 1.15 for door-to-balloon intervals of 61 to 120 min, 1.41 for 121 to 150 min and 1.62 for 151 to 180 min.

The study by de Boer et al. (6) raises several perplexing practical issues, which are inseparable from broader questions about the current state of primary angioplasty in the U.S. Primary angioplasty ideally depends on a systematic, integrated approach to emergency care of AMI patients, from initial treatment and triage by the emergency medical system through timely emergency department response to the simultaneous availability of an angiography suite, its staff of technologists, nurses and assistants and a high-volume interventional cardiologist. Like an eclipse, this perfect alignment is a wonderful event when it occurs, but it occurs rarely. Virtually no American hospital reserves a separate angiography suite for emergencies, so scheduling delays are common even during working hours; angioplasty staff are not maintained on-site 24 h a day, so on nights and weekends on-call staff must be summoned from home. Even at large teaching institutions, American medicolegal concerns preclude the apparent practice by de Boer et al. (6) of using senior trainees to begin interventional procedures immediately, without waiting for attending staff. As a result, angioplasty for AMI remains a slow happenstance treatment. In the Cannon et al. (14) analysis of data from the NRMI, only 8% of patients had a door-to-balloon interval of <60 min, the median in the study of de Boer et al. (6).

One question raised by the findings of de Boer et al. (6) is whether, given the wretchedly delayed practice of primary angioplasty in much of the world, their study can be fairly extrapolated to other systems. The available data do not permit an authoritative answer but they allow an educated guess. Even assuming an angioplasty mortality of about 8% in patients >75 years treated within 60 min and the multivariate odds ratio of 1.6 reported by Cannon et al. (14) for patients treated between 151 and 180 min after arrival, there would still be substantial net benefit for angioplasty compared to thrombolytic mortality of 18%. Randomized trial data focusing specifically on elderly patients with ST-elevation MI are urgently needed, but in its absence the preponderance of the evidence would seem to favor primary angioplasty over thrombolysis for patients >75 years at hospitals with skilled acute angioplasty capability, even if angioplasty involves summoning staff from home. The same cannot be said for younger ST-elevation patients without thrombolytic contraindications, for whom prolonged delay for primary angioplasty is commonplace and unjustifiable.

Only about 40% of patients >75 years with ST-elevation MI are treated at high volume hospitals with on-site angioplasty capability (15). Thus, the second question raised by the findings of de Boer et al. (6) is whether elderly

patients who present to hospitals without angioplasty capability should be treated with intravenous thrombolytics or with emergent transfer to a tertiary center, in conjunction with a temporizing cocktail of aspirin, heparin, clopidogrel and a glycoprotein IIb/IIIa inhibitor. Since the door-to-balloon time for interhospital transfer often exceeds 3 h, this question compares the much-diminished benefit of late mechanical reperfusion (together with risk from ambulance transfer) with the benefit or hazard of thrombolytic therapy in patients >75 years, which is unknown (16).

Until randomized trial data are available comparing thrombolytic therapy with delayed percutaneous intervention in patients >75 years old, a nuanced, commonsense approach seems reasonable. In urban areas where very rapid transfer for immediate angioplasty is feasible, emergency transfer can avoid the risks of thrombolysis. For other hospitals, despite misgivings about the safety and effectiveness of thrombolytic therapy in the elderly, randomized trial evidence probably should govern treatment for patients who present with widespread ST elevation, anterior MI or left bundle branch block within perhaps 4 h of the onset of sustained symptoms and without cardiogenic shock. For elderly patients who present later, in whom the potential benefit of thrombolytic therapy is dramatically diminished and the risk is unchanged, and for those who have good left ventricular function and small, well tolerated inferior or lateral infarctions, emergency transfer for mechanical reperfusion may be more appropriate. Patients with cardiogenic shock have shown no benefit from thrombolytic therapy (17) and should be immediately transferred for mechanical reperfusion.

As a practical matter, timely primary angioplasty for patients >75 years does not occur in isolation, without equally prompt treatment for younger patients. Analyses of 1994 to 1998 data from the NRMI (13) suggest that roughly one-third of U.S. patients who receive reperfusion therapy at hospitals with angioplasty capability undergo primary angioplasty, a proportion that can only have increased in the intervening years. Less than one-third of these patients have a door-to-balloon interval of <90 min, the standard of current American College of Cardiology/American Heart Association guidelines, which themselves reflect an implicit compromise between the remarkable benefit of times <60 min and estimates of political and logistical feasibility. Nearly half of primary angioplasty patients nationwide have an interval >120 min, an unconscionable delay in patients otherwise eligible for thrombolytics. Both randomized and observational data increasingly suggest that primary angioplasty involves a Faustian bargain, providing a substantial mortality advantage compared to thromboytic treatment for patients with short door-to-balloon times and a survival disadvantage for patients with delayed angioplasty, such as those who present at night and on weekends. This disparity is the most likely reason for the meager angioplasty benefit found in GUSTO IIb (8) compared to smaller antecedent trials. The axiom that "time is muscle" applies equally to thrombolytic and mechanical reperfusion.

Most cardiologists, if they personally had an acute anterior MI in an urban area, would want to be taken by ambulance directly to a high volume hospital with an empty table in the angiography suite, an experienced staff on-site, a high volume interventionalist in attendance and a median door-to-balloon time of <60 min. Although such an integrated emergency system does not now exist, it might halve the 30-day mortality from MI, as the study by de Boer et al. (6) suggests. The aggregate data supporting such a system vastly exceed the evidence that was used to develop policy for regional trauma centers decades ago: about 60% of MI patients are brought to the emergency department by ambulance and such patients are a very high risk group, with nearly three times the mortality of patients who arrive via other transportation (18). Studies too numerous to fully cite have shown better outcomes at high volume hospitals (13,15), by high volume interventionalists (19,20) and with short door-to-balloon times (11,14). In most urban and suburban areas, hospitals are clustered so closely that transport delays would be trivial (15), although the safety of longer transport has not been tested. Yet nothing has been done and very little has been said.

The unspoken reason for this remarkable inertia is economic self-interest, together with a dearth of policy leadership and of large clinical trials. Emergency medical system administrators have demonstrated little interest in telemetered 12-lead electrocardiograms, field triage criteria and increased helicopter transportation or extended ambulance run times to tertiary hospitals. Community hospital administrators, emergency department directors and cardiologists are unlikely advocates for field triage directly to tertiary facilities, which might reduce local occupancy and procedural revenue. Administrators at tertiary hospitals, already straining to staff angiography suites during regular hours, cannot afford empty emergency angiography suites and on-site staff 24 h a day. And the pharmaceutical industry, the sponsor of nearly all large-scale clinical research in AMI, would not benefit from integrated health care delivery. The status quo benefits everyone but the patient.

The result has been an unhappy impasse. There has been a movement to perform primary angioplasty at hospitals without bypass surgery, thus providing economic incentives to community hospitals and physicians while perpetuating the belated practice of primary angioplasty that already occurs at many tertiary hospitals. The economies of scale at large centers are unarguable: no community hospital can afford to maintain a standby angiography suite for emergency cases or on-site 24-h staffing, prerequisites for timely primary angioplasty. Common sense and observational evidence also suggest that effective primary angioplasty depends not only on the experience of the interventional cardiologist but also on the training, expertise and systematic integration of the entire health care team, including the emergency medical system, the emergency department, the

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catheterization laboratory and the coronary care unit, which are impossible to maintain without volume and specialization.

The ideal solution, pioneered decades ago by trauma surgeons and used for coronary care in some European cities, probably is a system that combines field triage, direct transportation of specified patients to designated cardiac centers, 24-h on-site staffing by an interventional team and guaranteed return to local practitioners for long-term follow-up. Building such a system within acute care cardiology—a largely fee-for-service specialty that has been notably refractory to regulation and integration—is a formidable task. Clinical research in AMI has long focused on small incremental benefits from drugs and devices, while neglecting the huge potential benefit of health system integration and timely primary angioplasty.

The clinical trial agenda is simple. In light of the findings of de Boer et al. (6), there is a desperate need for definitive, community-based, multicenter trials comparing intravenous thrombolytic treatment with primary percutaneous transluminal coronary angioplasty in elderly patients, both within tertiary hospitals and after emergent transfer from community to tertiary centers. The next priority involves a paradigm shift from drugs and devices within the current fragmented system of care to health system integration, beginning with the emergency medical system. Since a minority of chest pain patients actually have an AMI, derivation and validation of field triage criteria to identify high-risk patients are urgently needed, along with quantitative assessment of any risks from longer transport time. Such studies would lay the groundwork for a large, randomized, community-based trial comparing field triage of high-risk AMI patients directly to 24-h angioplasty centers with transportation to the nearest hospital for thrombolytic treatment if indicated.

The potential benefit of an integrated system for AMI patients may seem self-evident to some, but sound public policy and political reality both require rigorous research. Such studies are unlikely to occur without targeted requests for proposals from the National Institutes of Health. Research on integrated health care delivery systems for AMI patients is long overdue.

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